Stereospecific and Stereoselective Synthesis of β-Oximino and β-Hydroxylamino Sulfoxides

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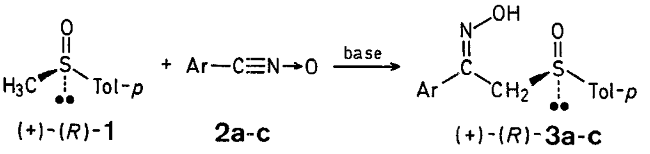
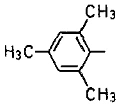
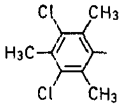
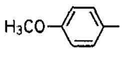
α-Functionalized sulfur compounds play a relevant role in organic synthesis; among these, optically active sulfoxides are of special interest in a number of stereoselective processes[1,2]. Two approaches have been devised for their preparation, involving either carbon-sulfur or carbon-carbon bond formation. The latter route implies the reaction of an optically active α-sulfinylcarbanion with electrophiles such as carboxylates, sulfinates, nitriles, carbonyl derivatives, or Schiff bases[1,2].

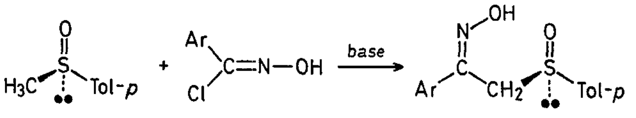
Surprisingly, no example of optically active α-functionalized sulfoxides derived by reaction of α-metallated sulfoxides with 1,3-dipoles has been reported so far[3]. We here describe the first example of such a process, namely the formation of optically active β-oximino sulfoxides 3 from nitrile oxides[6] 2 and methyl tolyl sulfoxide (1).



(+)-(R)-1 2a-c (+)-(R)-3a-c

2,3	a	b	c
Ar			

Reaction of enantiomerically pure (+)-(R)-p-tolyl methyl sulfoxide (1)[1,2] with lithium diisopropylamide and subsequent addition of the appropriate nitrile oxide 2 afforded optically active products 3 in good to excellent yield (Method A). Alternatively, the nitrile oxides 2 were prepared *in situ* by reaction of easily available benzohydroximinoyl chlorides[8] 4 and lithium diisopropylamide (Method B). By this route, which constitutes a method for the sulfurization of oximes, compounds 3a, c, and d (Ar = C_6H_5) could be prepared in 70–80% yield (Table 1).



(+)-(R)-1 4a-c (+)-(R)-3a-c

The optically active β-oximino sulfoxides (3) obtained are enantiomerically pure, as shown by ^{1}H-N.M.R. spectroscopy with the aid of the chiral shift reagent Eu(hfc)$_3$ in the case of compound 3d. Moreover, since the ligands at sulfur are not involved in the reaction, the absolute configuration, (+)-(R), can be directly assigned to compounds 3a-d on the basis of the (+)-(R) absolute configuration of 1. This stereoselective reaction is also stereospecific, only one of the two possible (E/Z)-stereoisomers being generally formed. In our opinion the preferred one is the (Z)-isomer because of the possibility of hydrogen bond formation between the oximino and the sulfoxide groups to give a seven-membered cyclic structure for compounds 3. The conformational rigidity of the system is clearly shown by the short relaxation times for both the methylene and the oximino carbons (0.4 and 6.9 sec, respectively), in agreement with previous reports[9,10].

Only in the case of 3b could minor amounts of the (E)-isomer be detected and no clear-cut evidence has been obtained to account for this behaviour. β-Oximino sulfoxides (Z)-3b and (E)-3b showed for the methylene carbons and protons (AB system) two different signals at δ = 60.2 ppm and 3.8 ppm, and δ = 64.8 ppm and 4.0 ppm, respectively (in 20 : 1 chloroform-d/pyridine).

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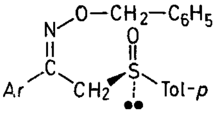
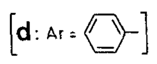
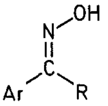
The assignment of the structure was supported by alkylation experiments carried out on compounds **3** to afford the *O*-benzylated products **5a-d** (Table 2).



(+)-(*R*)-**5a-d**

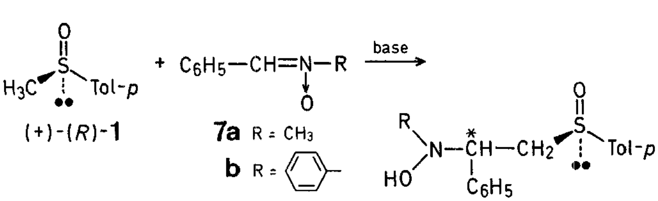




6 R = H, alkyl

It has been shown[11] that alkylation of oximes depends on their configuration: *O*-alkylation is predominant for the (*Z*)-form, while *N*-alkylation is more likely for the (*E*)-form. Namely, in compounds such as **6**, alkylation at oxygen prevails. Indeed, when we reacted *β*-oximino sulfoxides **3a-d** with benzyl bromide under phase transfer conditions, *O*-benzyl derivatives **5** were isolated in 49–83% yield, the yield being higher in the case of less sterically hindered substrates.

The reactions of *α*-sulfinylcarbanions derived from **1** with nitrones **7** afford optically active hydroxylamines **8a-c** (Table 3).



Also in this case the absolute configuration (*R*) at sulfur can be directly assigned to compounds **8**, since the reaction does not affect the chiral sulfoxide moiety in the conversion **1**→**8**. A new chiral center is formed and the reaction is definitely stereoselective, one of the two epimers being predominant. The diastereomeric ratio, as determined by ^{1}H-N.M.R. is 75:25, 82:18, and 100:0, in the case of **8a**, **8b**, and **8c**, respectively. Thus, chiral discrimination is very high, and increases with increasing bulkiness of the R residue of the nitrone. The enantiomeric purity at sulfur in compounds **8a-c** could not be determined directly by ^{1}H-N.M.R. spectroscopy with the aid of various chiral shift reagents. However, it is very likely that also in this reaction the chirality at the sulfoxide group is totally retained. The isolation of a diastereomerically homogeneous product, i.e. **8c**, strongly sustains this hypothesis.

The high degree of *β*-stereoselectivity observed in the reaction leading to **8a-c** prompted us to examine the reaction of a sulfoxide which could also give rise to *α*-asymmetric induction. Therefore we reacted optically active ethyl *p*-tolyl sulfoxide (+)-(*R*)-**9** with *N*-*t*-butylphenylnitrone (**7c**) to give the hydroxylamino sulfoxide **10** (mixture of two epimers in a 6:1 ratio) in 60% yield.

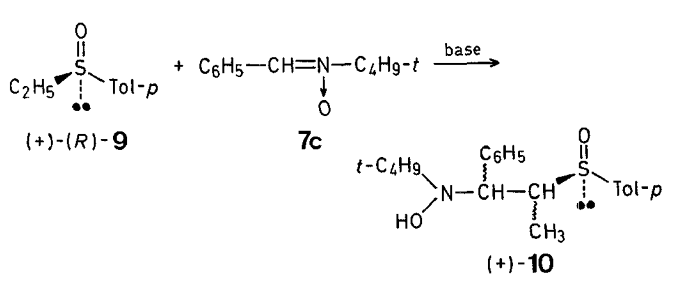


Table 1. Optically Active *β*-Oximino Sulfoxides (+)-(*R*)-**3**

Product	Method	Yield [%]	m.p. [°C]	$[\alpha]_D^{25}$ (*c* 1, $CHCl_3$)	Molecular formula[a]
3a	A	78	144°	+301°	$C_{18}H_{21}NO_2S$
3a	B	71	144°	+303°	(315.4)
3b	A	55[b]	172°	+273°[c]	$C_{18}H_{19}Cl_2NO_2S$ (384.3)
3c	A	78	135°	+ 53.8°[c]	$C_{16}H_{17}NO_3S$
3c	B	71	135°	+ 54.8°[c]	(303.4)
3d	B	80	116°	+ 46.0°[c]	$C_{15}H_{15}NO_2S$ (273.3)

[a] Satisfactory microanalyses obtained: C ±0.31, H ±0.11, N ±0.14.

[b] Together with ~15% of the (*E*)-isomer.

[c] (*c* 1, ethanol).

Table 2. *O*-Benzylated *β*-Oximino Sulfoxides (+)-(*R*)-**5**

Product	Yield [%]	m.p. [°C]	$[\alpha]_D^{25}$ (*c* 1, $CHCl_3$)	Molecular formula[a]
5a	54	wax	−44.4°	$C_{25}H_{27}NO_2S$ (405.6)
5b	49	wax	−36.0°	$C_{25}H_{25}Cl_2NO_2S$ (474.4)
5c	77	75–80°	−18.6°	$C_{23}H_{23}NO_3S$ (393.5)
5d	83	wax	−25.5°	$C_{22}H_{21}NO_2S$ (363.5)

[a] Satisfactory microanalyses obtained: C ±0.40, H ±0.15, N ±0.16.

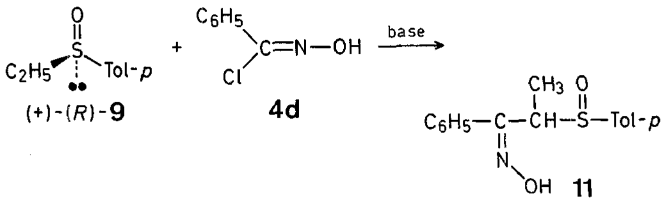
Table 3. Optically Active *β*-Hydroxylamino Sulfoxides **8**

Product	Yield [%]	m.p. [°C]	$[\alpha]_D^{25}$ (*c* 1, $CHCl_3$)	Molecular formula[a]
8a	85	97–100°	+ 64.3°	$C_{16}H_{19}NO_2S$ (289.4)
8b	77	178°	+236°	$C_{21}H_{21}NO_2S$ (351.5)
8c	84	152°	+138°	$C_{19}H_{25}NO_2S$ (331.5)

[a] Satisfactory microanalyses obtained: C ±0.33, H ±0.15, N ±0.13.

In principle, this reaction could lead to eight stereoisomers. However, as discussed above, the reaction should proceed with complete retention of chirality at sulfur. This was confirmed by ^{1}H-N.M.R. spectroscopy with the aid of the chiral shift reagent Eu(hfc)$_3$ (see experimental). Furthermore, the carbon atom *β* to the sulfoxide group should be diastereomerically pure (as in the case of **8c**). Thus, the observed 6:1 epimer ratio, in our opinion, reflects the extent of induction at the carbon atom directly linked to the sulfoxide.

For sake of comparison, we also examined the reaction of racemic **9** with phenyl nitrile oxide, generated *in situ* from the corresponding hydroximinoyl chloride **4d**, to give the *β*-oximino sulfoxide **11** as a mixture of isomers in a 13:1 ratio.



These two isomers give rise to different signals in the ^{13}C-N.M.R. spectrum (solvent $CDCl_3$) for the new asymmetric carbon atom. The small difference in their chemical shift (0.3 ppm) clearly shows that the two isomers are very likely epimers at carbon, rather than (*E*/*Z*)-isomers, for which a much larger difference can be expected [see above, in the case of **3b**]. Thus, also in the case of sulfoxide **11** a high degree of stereoselection is achieved.

The optically active sulfoxides **1** and **9** were prepared according to Ref.[10]:

(+)-(*R*)-**1**; $[\alpha]_D^{25}$: +189° (*c* 1, $CHCl_3$); Ref.[12], $[\alpha]_D^{25}$: +189.2° (*c* 1, $CHCl_3$);

Racemic **1**; m.p. 42–43 °C; Ref.[13], m.p. 42–43 °C;

(+)-(*R*)-**9**; $[\alpha]_D^{25}$: +189° (*c* 1, acetone); Ref.[12], $[\alpha]_D^{25}$: +189° (*c* 1, acetone);

Racemic **9**; b.p. 104 °C/0.4 torr; Ref.[14], b.p. 104–105.5 °C/0.4 torr.

Nitrile oxides **2**, benzohydroximinoyl chlorides **4**, and nitrones **7** were prepared according to Refs.[8,15,16]. *4-Methoxyphenyl nitrile oxide* (**2c**) was previously unknown; m.p. 64–65 °C (from ethanol).

$C_8H_7NO_2$	calc.	C 64.43	H 4.70	N 9.40
(149.2)	found	64.46	4.60	9.35

Optically Active β-Oximino Sulfoxides 3; Typical Procedures:

Method A: (+)-(*R*)-*p*-Tolyl methyl sulfoxide (**1**; 0.308 g, 2.0 mmol) in anhydrous tetrahydrofuran (5 ml) is added dropwise to a cooled (−78 °C), stirred solution of lithium diisopropylamide, prepared from diisopropylamine (0.58 ml, 4.0 mmol) and *n*-butyllithium (2.66 ml of a 1.5 normal solution in hexane, 4.0 mmol) in tetrahydrofuran (5 ml). The mixture is allowed to reach −20 °C, cooled again to −78 °C, and treated with the nitrile oxide **2** (2.0 mmol) in tetrahydrofuran (10 ml). After 30 min stirring at −78 °C, the reaction is quenched with saturated ammonium chloride solution (5 ml) and the mixture warmed up to room temperature. The organic phase is separated, dried with sodium sulfate, filtered, and evaporated. The crude material is then chromatographed (silica gel; ether : light petroleum, 7 : 3) to give the pure products.

Method B: (+)-(*R*)-*p*-Tolyl methyl sulfoxide (**1**; 0.308 g, 2.0 mmol) in anhydrous tetrahydrofuran (5 ml) is added dropwise to a cooled (−78 °C) stirred solution of lithium diisopropylamide, prepared from diisopropylamine (0.86 ml, 6.0 mmol) and *n*-butyllithium (4.0 ml of 1.5 normal solution in hexane, 6.0 mmol) in tetrahydrofuran (5 ml). The mixture is allowed to reach −20 °C, cooled again to −78 °C, and reacted with the benzohydroximinoyl chloride **4** (2.0 mmol) at −78 °C; the reaction is quenched and worked-up as described above.

Alkylation of β-Oximino Sulfoxides 3; Typical Procedure:

To a stirred mixture of the β-oximino sulfoxide **3** (2 mmol), dichloromethane (5 ml), 10% sodium hydroxide (1 ml), and benzyl bromide (0.48 g, 4 mmol), kept at room temperature, benzyltriethylammonium bromide (0.045 g, 0.2 mmol) is added. After 1 h stirring [48 h in the case of (**3b**)], water (15 ml) and dichloromethane (15 ml) are added to the mixture, the phases are separated, the organic phase is dried with sodium sulfate, and filtered. The crude mixture is purified by column chromatography (silica gel, ether) to give the products.

β-Hydroxylamino Sulfoxides 8 or 10; Typical Procedure:

(+)-(*R*)-Sulfoxide **1** or **9** (2.0 mmol) in anhydrous tetrahydrofuran (5 ml) is added dropwise to a cooled (−78 °C), stirred solution of lithium diisopropylamide, prepared from diisopropylamine (0.58 ml, 4.0 mmol) and *n*-butyllithium (2.66 ml of 1.5 normal solution in hexane, 4.0 mmol) in tetrahydrofuran (5 ml). The mixture is allowed to reach −20 °C, cooled again to −78 °C, and treated with the nitrone **7** (2.0 mmol) in tetrahydrofuran (10 ml). The mixture is stirred for 30 min at −78 °C, quenched, and worked-up as described for the synthesis of compounds **3**. The products are purified by column chromatography (silica gel, ether).

1-(N-t-butyl-N-hydroxylamino)-1-phenyl-prop-2-yl p-tolyl sulfoxide (**10**); yield: 55%; m.p. 161–162°; $[\alpha]_D^{25}$: +81.0° (*c* 1, chloroform).

$C_{20}H_{27}NO_2S$	calc.	C 69.52	H 7.87	N 4.05
(345.5)	found	69.50	7.89	4.00

Racemic β-Oximino and β-Hydroxylamino Sulfoxides:

Racemic compounds were prepared as described above, but starting from racemic sulfoxides **1** and **9**.

Racemic **3d**; yield: 75%; m.p. 123–124 °C.

Compound **11**; yield: 70%; m.p. 140–141 °C.

$C_{16}H_{17}NO_2S$	calc.	C 66.86	H 5.96	N 4.87
(287.4)	found	66.85	5.98	4.87

Racemic **10**; yield: 60%; m.p. 164–166 °C.

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